Original Article

Gain of GAS5 reveals worse prognosis in kidney renal clear cell carcinoma and liver hepatocellular carcinoma from the Cancer Genome Atlas dataset

Jingjing Li[1,2,3#], Yan Li[4#], Xiaoshun He[1,2,3], Qiang Zhao[1,2,3]

[1]Organ Transplant Center, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; [2]Guangdong Provincial Key Laboratory of Organ Donation and Transplant Immunology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; [3]Guangdong Provincial International Cooperation Base of Science and Technology (Organ Transplantation), The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; [4]Department of Pathology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Contributions: (I) Conception and design: J Li, Q Zhao; (II) Administrative support: X He; (III) Provision of study materials or patients: J Li, Y Li; (IV) Collection and assembly of data: J Li, Y Li; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Qiang Zhao; Xiaoshun He. Organ Transplant Center, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China. Email: zhaoqiang_china@sina.com; gdtrc@163.com.

Background: The role of long non-coding RNA growth arrest-specific 5 (GAS5) in cancer development is controversial. The aim of this study was to evaluate the prognostic significance of GAS5 in kidney renal clear cell carcinoma (KIRC) and liver hepatocellular carcinoma (LIHC) from The Cancer Genome Atlas (TCGA) dataset and to explore its potential regulatory mechanism through data mining.

Methods: Expression of GAS5 and its clinical information within 14 kinds of cancers were obtained from TCGA dataset. The correlation between the expression of GAS5 and abhydrolase domain containing 2 (ABHD2) in KIRC and LIHC were analyzed through R2 website. The overall survival (OS) was assessed using the Kaplan-Meier method. Wilcoxon test was conducted to assess the DNA methylation of CpG sites of GAS5 or ABHD2 between normal and tumor sample in both KIRC and LIHC patients.

Results: Results showed GAS5 was significantly upregulated in KIRC and LIHC tissues compared with normal tissues, which was rarely seen in other cancers. High GAS5 expression was associated with poor overall survival (OS) in both KIRC and LIHC. Our study firstly confirmed a negative correlation between GAS5 and ABHD2 protein in both KIRC and LIHC. Methylation analysis showed that high GAS5 expression had lower DNA methylation status while low ABHD2 expression had higher DNA methylation status in both cancers.

Conclusions: Our research revealed that GAS5 was likely to function as an oncogene in both KIRC and LIHC, and negatively correlated with ABHD2. Furthermore, DNA hypomethylation might have an important effect on increased GAS5 transcription and reduced ABHD2 transcription in both cancers.

Keywords: Prognosis; growth arrest-specific 5 (GAS5); liver hepatocellular carcinoma; kidney renal clear cell carcinoma (KIRC); abhydrolase domain containing 2 (ABHD2)

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Introduction

Human cancer is a complex disease caused by the genetic and epigenetic alternations of two kinds of crucial genes: tumor suppressor genes and oncogenes (1). *p53*, one of the most famous tumor suppressor genes, controls DNA repair system and restrict chromosomal instability (2). While *KRAS*, as an essential oncogene, has been shown to promote cancer development and progression as well as influence the tumor microenvironment (3). However, some genes like *TGF*-β family members exert tumor suppressive effect early in tumorigenesis, but later they can lead to tumor progression and metastasis depending on signaling from growth factor receptors or activity of transcriptional regulators (4).

Being a long non-coding RNA and unable to encode protein, growth arrest-specific 5 (GAS5) has been reported to be a vital tumor suppressor and involved in apoptosis, proliferation, migration, invasion, cell cycle and metabolism of multiple cancers (5). Recent research reports that GAS5 suppressed the angiogenesis, invasion, and metastasis of colorectal cancer by inhibiting the activated Wnt/β - catenin signaling pathway (6). In addition, GAS5 could inhibit cervical cancer cell proliferation, migration and invasion through miR-21 (7). Overexpression of GAS5 in ovarian cancer cells restrained proliferation, and was associated with inflammasome formation and pyroptosis (8).

However, some studies have revealed that GAS5 has a certain ability to promote cancer. Li *et al.* have revealed that GAS5 expression was increased in esophageal cancer cells and miR-301a was sponged to alleviate its pro-oncogene effects (9). Previous study showed that ectopic expressed GAS5 displayed an anti-apoptosis effect in liver cancer cell lines (10).

In this research, we analyzed the expression of GAS5 through data mining in The Cancer Genome Atlas (TCGA) datasets, and explored its prognostic value and potential regulatory mechanism in both kidney renal clear cell carcinoma (KIRC) and liver hepatocellular carcinoma (LIHC).

We present the following article in accordance with the MDAR reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-2221).

Methods

Data from the TCGA dataset

Expression of GAS5 in most cancer types represented in the form of log2(TPM + 1) from the University of California Santa Cruz (UCSC) Xena Project were obtained from GEPIA (http://gepia.cancer-pku.cn/) (11), only those groups had more than 10 samples were included. And the correlation between GAS5 and ABHD2 as well as the survival data of patients (updated to June 2019) with KIRC and LIHC were downloaded from R2 website related to TCGA program (http://r2platform.com). DNA methylation data of GAS5 and abhydrolase domain containing 2 (ABHD2) (measured by the Infinium Human Methylation 450 BeadChip) in LIHC and KIRC were downloaded from the TCGA Wanderer (http://www.maplab.cat/wanderer) (12). All these data can be downloaded for free from the above public website. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analysis

One-way ANOVA was used to detect differences for comparisons. Survival curves were generated by the Kaplan Scan by using median or scan as a cutoff in assessing whether GAS5 or ABHD2 has the potential to separate patient survival and test the P value in a log-rank test. Wilcoxon test was conducted to assess the DNA methylation of CpG sites of GAS5 or ABHD2 between normal and tumor sample in both KIRC and LIHC patients. $P<0.05$ was considered as statistically significant.

Results

Expression of GAS5 in most cancer types from TCGA program

To explore the expression of GAS5 in different kinds of cancers, we obtained RNA-sequencing data from TGCA in GEPIA (*Figure 1*). Nine types of tumor were excluded because they didn't have enough normal tissue samples. By comparing the expression level of GAS5 between 14 kinds of cancer tissues and their normal tissues, we found that the expression of GAS5 had no significant difference in most of them, but was significantly upregulated in KIRC and LIHC (fold change >2, $P<0.01$).

High GAS5 expression is associated with poor overall survival (OS) in both KIRC and LIHC

In order to validate its prognostic significance, we compared the association between GAS5 and OS using Kaplan-Meier survival curves (*Figure 2*). In KIRC patients, we separated them by the median expression of GAS5 into two groups, and the low GAS5 expression groups (n=266) had much

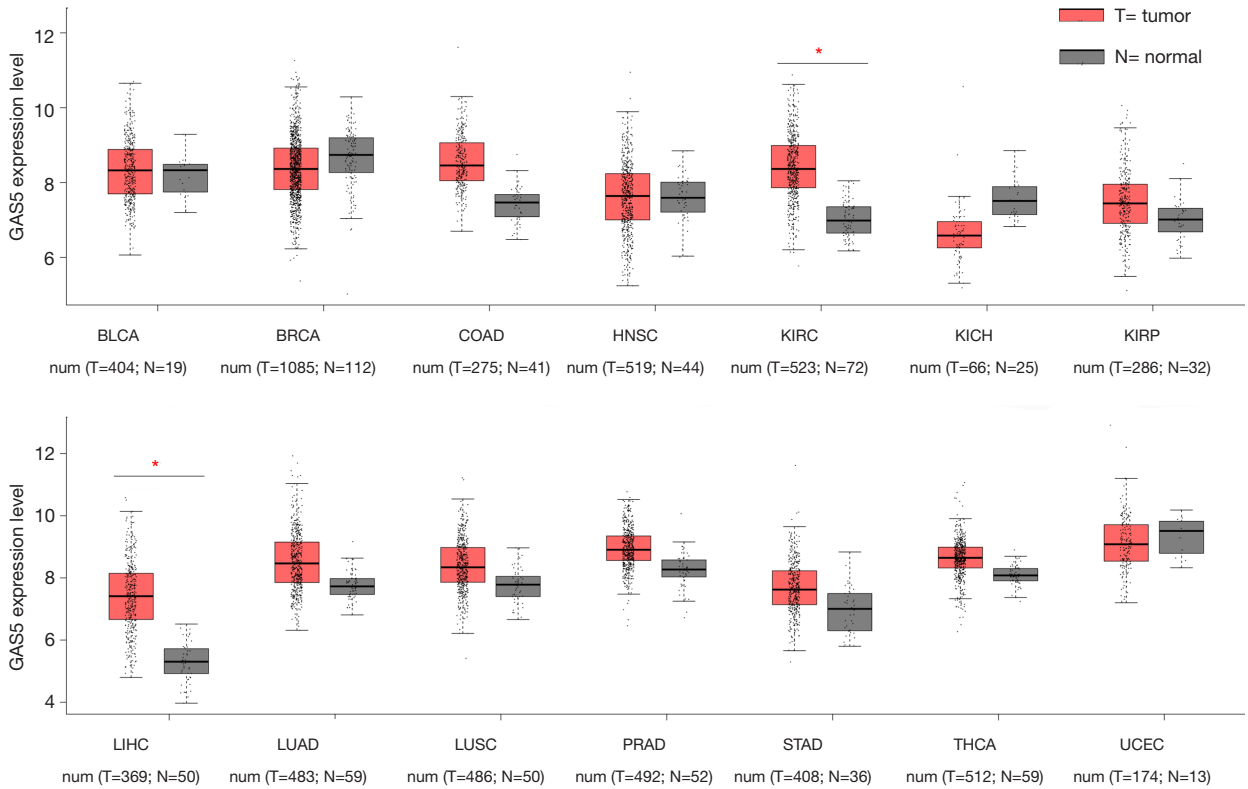


Figure 1 Expression of GAS5 in 14 kinds of cancers through TCGA program. *, P<0.01. GAS5, growth arrest-specific 5; TCGA, The Cancer Genome Atlas; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; COAD, colon adenocarcinoma; HNSN, head and neck squamous cell carcinoma; KICH, kidney Chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; num, number; PRAD, prostate adenocarcinoma; STAD, stomach adenocarcinoma; UCEC, uterine corpus endometrial carcinoma.

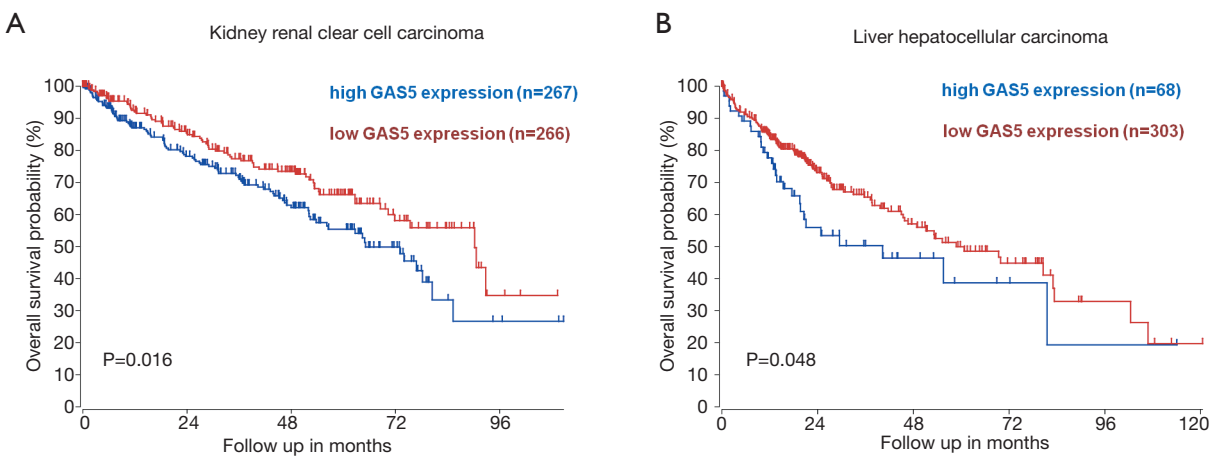


Figure 2 Kaplan-Meier curves of OS separated by the optimal cutoff of GAS5 expression in patients with KIRC (A) and LIHC (B). OS, overall survival; GAS5, growth arrest-specific 5; KIRC, kidney renal clear cell carcinoma; LIHC, liver hepatocellular carcinoma.

Table 1 Mini ontology analysis in KIRC

Group	InSet	Total	%	P
All	4,131	9,247	44.70	1
DNA repair	119	211	56.40	6.10E–04
Transcription factor	374	812	46.10	0.43
Apoptosis	315	633	49.80	0.01
Cell cycle	254	492	51.60	1.90E–03
Development	698	1,602	43.60	0.37
Different	299	682	43.80	0.66
Drugtarget	506	1,151	44.00	0.63
Kinase	334	649	51.50	5.00E–04
Membrane	2,025	4,889	41.40	4.70E–06
Signal transduction	1,258	3,026	41.60	6.00E–04
Transcription regulator activity	608	1,208	50.30	7.70E–05
Transcriptional repressor activity	98	180	54.40	8.40E–03

KIRC, kidney renal clear cell carcinoma.

longer OS than their respective high expression groups (n=267) (*Figure 2A*, P=0.016). In LIHC patients, we used scan as a cutoff to separated them into two groups, and the high GAS5 expression groups (n=68) had shorter OS than their low expression groups (n=303) (*Figure 2B*, P=0.048).

ABHD2 was highlighted between those genes co-related with GAS5 in both cancers

New biologically relevant hypotheses can be generated when we find out the related genes. Therefore, we performed HugoOnce mode analysis in R2 software to explore the relations of other genes with GAS5 in KIRC and LIHC. It summarized the results of a mini ontology analysis (*Tables 1*,*2*). In KIRC, those genes were involved with the process of DNA repair, apoptosis, cell cycle, kinase, membrane, signal transduction, transcription regulator activity and transcriptional repressor activity; while in LIHC, they were involved with DNA repair, development, membrane, transcription regulator activity and transcriptional repressor activity. Among them, membrane groups had the most significant P value. As a membrane protein, ABHD2 was highlighted in both KIRC and LIHC when we listed the top 20 genes (*Tables 3*,*4*).

ABHD2 is negatively correlated with GAS5

Data mining in R2 confirmed a moderately negative correlation between the expression of ABHD2 and GAS5 in both KIRC (R=–0.501, P<0.001) and LIHC (R=–0.584, P<0.001) cancers (*Figure 3A*,*B*). Also, we wanted to verify the association of ABHD2 with OS of those cancer patients. Thus, the low ABHD2 expression groups had significantly shorter OS than their respective high expression groups in KIRC (*Figure 3C*, P=0.00059) and LIHC (*Figure 3D*, P=0.026) patients.

DNA methylation might regulate the transcription of GAS5 and ABHD2 in both cancers

To further examine the potential regulatory effect of DNA methylation on GAS5 and ABHD2 expression, we compared their status in the TCGA Wanderer. *Figure 4A*,*B* showed that 12 CpG sites of GAS5 (cg03044573, cg16290996, cg17025683, cg07177756, cg05396044, cg06704773, cg04102126, cg02955369, cg17868533, cg16905926, cg17170111, cg10578779) were significantly hypermethylated in the normal tissues compared with tumor tissues. In comparison, *Figure 4C*,*D* showed that 11 CpG sites of ABHD2 (cg04788288, cg16663533, cg27351321,

Table 2 Mini ontology analysis in LIHC

Group	InSet	Total	%	P
All	4,506	9,184	49.10	1
DNA repair	121	211	57.30	0.02
Transcription factor	394	811	48.60	0.78
Apoptosis	333	633	52.60	0.07
Cell cycle	263	492	53.50	0.05
Development	738	1,600	46.10	0.02
Different	318	681	46.70	0.22
Drugtarget	575	1,151	50.00	0.54
Kinase	342	649	52.70	0.06
Membrane	2,243	4,828	46.50	2.90E–04
Signal transduction	1,436	2,967	48.40	0.47
Transcription regulator activity	611	1,207	50.60	0.28
Transcriptional repressor activity	103	180	57.20	0.03

LIHC, liver hepatocellular carcinoma.

Table 3 Top 20 genes related with GAS5 in KIRC

HUGO	Function	R	P	HUGO	Function	R	P
ZFAS1	–	0.791	2.2E–113	*SNX19*	Signal	–0.576	1.5E–46
RPL5	–	0.784	5.5E–110	*AP1G1*	Membrane	–0.536	3.8E–39
RPS8	–	0.765	1.2E–101	*FICD*	–	–0.518	3.1E–36
RPS18	–	0.749	6E–95	*USP9X*	–	–0.51	6E–35
EPB41L4A-AS1	–	0.738	8.1E–91	*PEX26*	Membrane	–0.507	2.5E–34
RPS3	–	0.731	3.4E–88	*GLYR1*	–	–0.505	4.9E–34
RPL31	–	0.72	3.2E–84	*AAK1*	Kinase	–0.505	4.2E–34
RPL12	–	0.714	3.7E–82	*ADAT1*	–	–0.504	6.1E–34
RPL18	–	0.712	9.6E–82	*ANKFY1*	Membrane	–0.502	1.4E–33
RPL11	–	0.708	3.8E–80	*ABHD2*	Membrane	–0.501	2E–33
RPS6	–	0.699	1.9E–77	*KIAA0232*	–	–0.498	5.8E–33
RPS24	–	0.688	5.6E–74	*UGGT1*	–	–0.489	1.2E–31
RPL34	–	0.687	8.5E–74	*ITPR2*	Membrane	–0.488	1.6E–31
RPL4	–	0.684	8.2E–73	*NDUFS1*	Apoptosis	–0.484	7.1E–31
RPL38	–	0.684	8.9E–73	*DYNLL2*	–	–0.484	5.6E–31
RPL10	–	0.678	4.1E–71	*NSF*	–	–0.48	2.4E–30
LRRC75A-AS1	–	0.678	6.1E–71	*GSK3B*	Apoptosis	–0.48	2.3E–30
RPL10A	–	0.677	7.9E–71	*SMC1A*	DNArepair	–0.476	9.5E–30
RPL30	–	0.676	1.7E–70	*ATP10D*	DNArepair	–0.476	8.1E–30
RPL19	–	0.675	2.80E–70	DIRC2	Membrane	–0.476	8.3E–30

'–': The function of these proteins were not mentioned in the R2 websites. GAS5, growth arrest-specific 5; KIRC, kidney renal clear cell carcinoma.

Table 4 Top 20 genes related with GAS5 in LIHC

HUGO	Function	R	P	HUGO	Function	R	P
ZFAS1	–	0.792	3.8E–79	*RSC1A1*	–	–0.647	1.2E–43
RPS24	–	0.764	1.9E–70	*SCP2*	–	–0.646	1.4E–43
RPS3	–	0.764	2.2E–70	*AP5M1*	–	–0.642	8.1E–43
RPS18	–	0.762	9.9E–70	*LONP2*	–	–0.634	2E–41
RPL31	–	0.752	5.2E–67	*DDI2*	–	–0.632	4.8E–41
RPL6	–	0.752	7.4E–67	*ATP11C*	Membrane	–0.626	3.8E–40
SNHG6	–	0.75	2.4E–66	*WDR7*	–	–0.622	1.9E–39
RPL14	–	0.748	5.1E–66	*SLC41A2*	–	–0.622	2.3E–39
RPL8	–	0.746	1.8E–65	*ERCC4*	DNArepair	–0.618	7.6E–39
RPL23	–	0.74	1.1E–63	*ALDH6A1*	Drugtarget	–0.61	1.6E–37
RPL37A	–	0.739	1.4E–63	*SLC35A3*	Membrane	–0.609	2.2E–37
RPLP0	–	0.738	2.3E–63	*SLC30A4*	Membrane	–0.602	2.3E–36
RPS10	–	0.738	2.7E–63	*MYLK*	Kinase	–0.601	3.5E–36
RPL32	–	0.736	8.9E–63	*APOOL*	–	–0.594	3.7E–35
RPS7	–	0.733	4.7E–62	*ZYG11B*	–	–0.593	6.4E–35
EPB41L4A-AS1	–	0.732	8.7E–62	*CPED1*	–	–0.592	8.6E–35
GNB2L1	Signal	0.731	2.2E–61	*EFCAB14*	–	–0.588	3.2E–34
RPSA	Membrane	0.729	7.9E–61	*HERC3*	–	–0.586	6.2E–34
RPL37	–	0.725	6.2E–60	*ABHD2*	Membrane	–0.584	1.3E–33
TAF1D	–	0.725	7.7E–60	*AGL*	–	–0.583	1.7E–33

'–': The function of these proteins were not mentioned in the R2 websites. GAS5, growth arrest-specific 5; LIHC, liver hepatocellular carcinoma.

cg03025135, cg12850396, cg25156843, cg10173620, ch.15.1525362R, cg13460556, cg23124613, cg03432151) were significantly hypomethylated in the normal tissues compared with tumor tissues. These results inferred that DNA methylation might regulate their transcriptions in both cancers.

Discussion

Published data showed that the expression of GAS5 was decreased in renal cell carcinoma cell lines (13). Similarly, reduced GAS5 expression was detected in clear cell renal cell carcinoma tissues and independently correlated with poor disease free survival of patients; their data revealed that GAS5 may function as a competing endogenous RNA (ceRNA) to positively regulate hZIP1 by sponging miR-223 (14). Latest research reported GAS5 downregulation promoted responsive renal cell carcinoma cells resistant to sorafenib treatment through miR-21/SOX5 axis (15). However, our research demonstrated that the mRNA level of GAS5 was significantly increased more than two folds in TCGA-KIRC dataset, probably because TCGA-KIRC dataset had much more samples than those previous studies. Moreover, high GAS5 expression was associated with poor OS, which predicted that GAS5 could be a prognostic marker for KIRC patients.

There are contrary results about GAS5 association with liver cancer. Two previous studies reported that downregulation of GAS5 was detected in liver cancer tissues compared with adjacent tissues and its reduction was associated with poor OS (16,17). Some other studies revealed that GAS5 could suppress metastasis via miR-21 (18) and inhibit the epithelial mesenchymal transition (EMT) of liver cancer cells (19). In contrary, knockdown

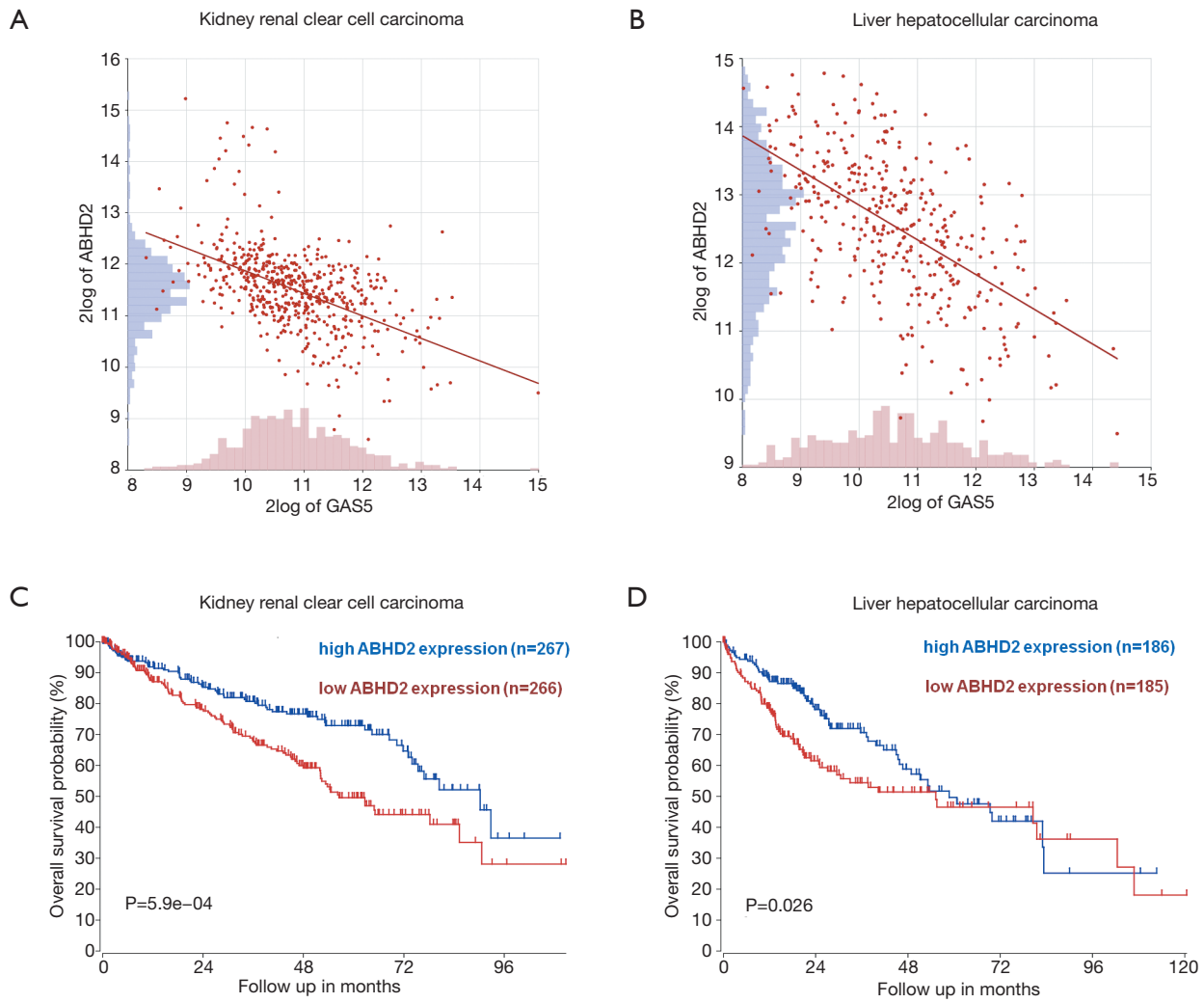
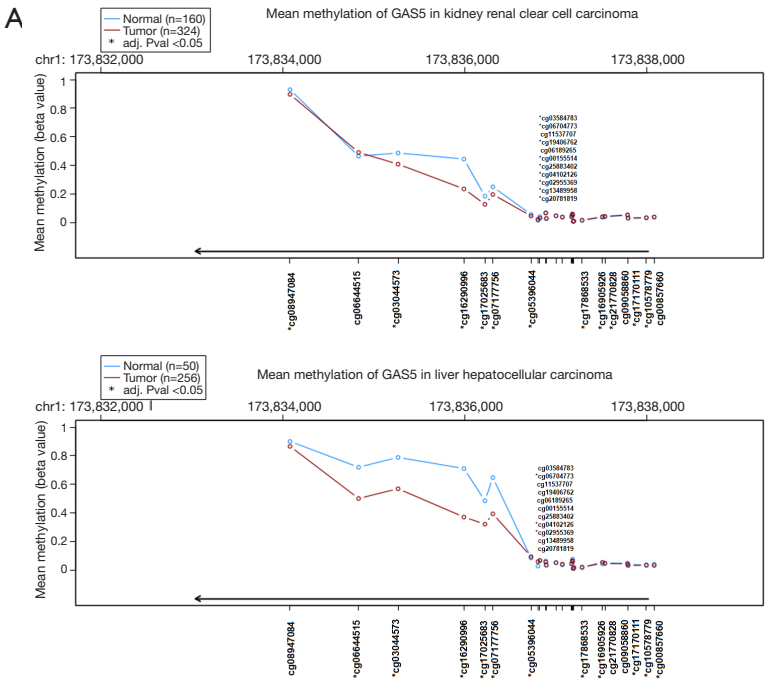


Figure 3 Relationship between ABHD2 and GAS5 in KIRC (A) and LIHC (B) along with its prognosis in KIRC (C) and LIHC (D) cancer patients. ABHD2, abhydrolase domain containing 2; GAS5, growth arrest-specific 5; KIRC, kidney renal clear cell carcinoma; LIHC, liver hepatocellular carcinoma.

of GAS5 partially revert the anti-apoptosis effect in liver cancer cell lines (10). A bioinformatic analysis demonstrated that high GAS5 was an independent predictor of shorter relapse free survival rather than OS in TCGA-LIHC (20). In the contrary, when we used scan as a cutoff to separated LIHC patients into two groups, results showed that high GAS5 level was associated with poor OS.

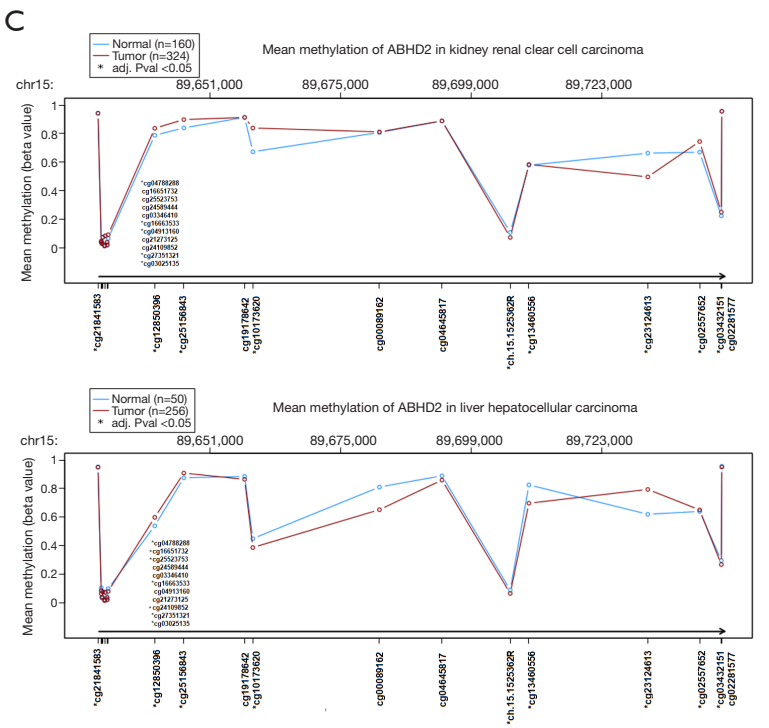
Therefore, we speculated that GAS5 might have its unique role and exert oncogenic effect in the development and progression of KIRC and LIHC. And, GAS5 might have different functions depending on different genetic backgrounds. In order to find out its new mechanism, we explored the correlated genes of GAS5. Results showed that GAS5 might be involved with DNA repair, development, apoptosis, cell cycle, kinase, membrane, signal transduction, transcription regulator activity and transcriptional repressor activity. Among them, ABHD2 was found to be negatively correlated with GAS5, and its low level could predict poor OS in KIRC and LIHC patients, which has never been reported before.

As a member of the α/β hydrolase superfamily, ABHD2 was reported to possess triacylglycerol (TAG) lipase along with ester hydrolysing capacity and regulate the lipid metabolism and signal transduction (21). ABHD2



B

GAS5 CpG sites	KIRC Methylation(mean±SD) Normal	KIRC Methylation(mean±SD) Tumor	KIRC Adjusted p value	LIHC Methylation(mean±SD) Normal	LIHC Methylation(mean±SD) Tumor	LIHC Adjusted p value
cg08947084	0.93±0.02	0.90±0.06	6.53E-15	0.90±0.04	0.87±0.12	0.31528
cg06644515	0.46±0.08	0.49±0.16	0.09031	0.72±0.07	0.50±0.20	4.90E-12
cg03044573	0.49±0.09	0.41±0.16	8.00E-12	0.79±0.09	0.57±0.26	6.29E-07
cg16290996	0.44±0.06	0.24±0.13	2.53E-49	0.71±0.10	0.37±0.26	2.26E-14
cg17025683	0.18±0.03	0.13±0.10	3.37E-37	0.49±0.09	0.32±0.27	0.0001
cg07177756	0.25±0.07	0.2±0.12	3.22E-17	0.65±0.13	0.39±0.32	2.09E-05
cg05396044	0.06±0.01	0.05±0.01	6.59E-21	0.08±0.04	0.09±0.11	1.55E-05
cg03584783	0.02±0.01	0.02±0.02	1.09E-08	0.03±0.02	0.06±0.11	0.11362
cg06704773	0.04±0.01	0.03±0.01	4.79E-30	0.07±0.03	0.07±0.10	1.29E-07
cg11537707	0.07±0.02	0.07±0.01	0.09031	0.06±0.01	0.06±0.02	4.90E-06
cg19406762	0.03±0.01	0.03±0.01	0.00315	0.03±0.01	0.03±0.02	0.19709
cg06189265	0.05±0.01	0.05±0.01	0.53225	0.05±0.01	0.05±0.05	3.34E-05
cg00155514	0.04±0.01	0.04±0.01	0.04813	0.04±0.01	0.04±0.02	0.07595
cg25883402	0.04±0.02	0.04±0.02	0.00179	0.05±0.01	0.04±0.01	0.34467
cg04102126	0.05±0.01	0.06±0.02	1.61E-05	0.06±0.01	0.07±0.01	0.00372
cg02955369	0.05±0.01	0.05±0.01	0.00492	0.08±0.05	0.06±0.02	0.00017
cg13489958	0.01±0.00	0.01±0.00	2.53E-13	0.01±0.00	0.01±0.01	0.35464
cg20781819	0.01±0.00	0.01±0.00	3.23E-12	0.02±0.05	0.01±0.01	0.64142
cg17868533	0.01±0.00	0.02±0.01	6.86E-08	0.02±0.01	0.02±0.00	0.00071
cg16905926	0.04±0.02	0.04±0.02	0.00179	0.04±0.02	0.05±0.02	0.01257
cg21770828	0.04±0.01	0.04±0.01	0.00012	0.05±0.01	0.05±0.01	0.08303
cg09058860	0.05±0.01	0.05±0.02	0.5545	0.05±0.01	0.04±0.01	0.00372
cg17170111	0.03±0.01	0.03±0.01	0.00253	0.04±0.01	0.03±0.01	2.73E-06
cg10578779	0.03±0.01	0.03±0.01	0.01967	0.04±0.01	0.03±0.01	0.0152
cg00857660	0.04±0.01	0.04±0.01	0.4311	0.04±0.01	0.03±0.01	2.68E-06



D

ABHD2 CpG Sites	KIRC Methylation(mean±SD) Normal	KIRC Methylation(mean±SD) Tumor	KIRC Adjusted p value	LIHC Methylation(mean±SD) Normal	LIHC Methylation(mean±SD) Tumor	LIHC Adjusted p value
cg21841583	0.94±0.02	0.94±0.06	9.69E-07	0.95±0.01	0.95±0.01	0.132261
cg04788288	0.04±0.01	0.04±0.04	2.93E-07	0.11±0.05	0.06±0.09	1.31E-14
cg16651732	0.04±0.01	0.05±0.03	0.441837	0.08±0.03	0.09±0.10	1.43E-05
cg25523753	0.03±0.01	0.03±0.01	0.726982	0.03±0.01	0.04±0.07	0.004582
cg24589444	0.03±0.01	0.03±0.01	0.915546	0.03±0.01	0.04±0.06	0.445078
cg03346410	0.07±0.01	0.07±0.01	0.441837	0.08±0.01	0.08±0.01	0.088738
cg16663533	0.01±0.00	0.01±0.01	1.05E-08	0.02±0.00	0.01±0.00	0.048555
cg04913160	0.01±0.00	0.02±0.00	9.82E-13	0.02±0.01	0.02±0.00	0.229178
cg21273125	0.08±0.02	0.08±0.03	0.912591	0.07±0.02	0.07±0.04	0.229178
cg24109852	0.04±0.01	0.04±0.01	0.668551	0.04±0.01	0.04±0.01	0.000302
cg27351321	0.02±0.00	0.02±0.02	2.20E-08	0.02±0.00	0.02±0.01	3.87E-06
cg03025135	0.07±0.02	0.09±0.05	3.84E-14	0.10±0.03	0.08±0.04	1.39E-06
cg12850396	0.79±0.13	0.84±0.13	1.35E-07	0.54±0.12	0.60±0.20	0.010719
cg25156843	0.84±0.05	0.90±0.09	7.93E-34	0.88±0.04	0.91±0.07	4.77E-10
cg19178642	0.91±0.02	0.91±0.03	0.441837	0.88±0.03	0.86±0.09	0.775096
cg10173620	0.67±0.05	0.84±0.13	4.03E-45	0.45±0.07	0.39±0.17	0.000302
cg00089162	0.81±0.07	0.81±0.07	0.441837	0.81±0.05	0.65±0.18	5.20E-08
cg04645817	0.89±0.04	0.89±0.05	0.56618	0.89±0.08	0.86±0.06	8.53E-07
ch.15.1525362R	0.11±0.03	0.07±0.04	1.08E-34	0.09±0.02	0.06±0.02	1.94E-10
cg13460556	0.58±0.06	0.58±0.21	0.026881	0.83±0.04	0.70±0.18	1.47E-05
cg23124613	0.66±0.13	0.50±0.16	1.11E-31	0.62±0.14	0.79±0.14	4.05E-11
cg02557652	0.67±0.05	0.74±0.15	4.31E-14	0.64±0.06	0.65±0.18	0.209792
cg03432151	0.22±0.05	0.25±0.05	1.91E-07	0.30±0.06	0.27±0.06	0.002594
cg02281577	0.96±0.01	0.96±0.01	0.56618	0.96±0.01	0.95±0.04	0.556577

Figure 4 CpG sites methylation status of GAS5 (A,B) and ABHD2 (C,D) in KIRC and LIHC patients. GAS5, growth arrest-specific 5; ABHD2, abhydrolase domain containing 2; KIRC, kidney renal clear cell carcinoma; LIHC, liver hepatocellular carcinoma.

deficient in aged mice led to reduction of alveolar type II cells and accumulation of macrophages in the lungs; in addition, ABHD2 could affect macrophage recruitment to atherosclerotic lesions. Thus, ABHD2 seemed to play a significant role in chronic diseases like emphysema and atherosclerosis (22,23). A study showed that knockdown of ABHD2 blocks hepatitis B virus propagation (24); while others reported that ABHD2 knockdown could reduce cell death by attenuating calcium release from the endoplasmic reticulum and mitochondrial calcium uptake in primary mouse lung fibroblasts stimulated with A23187 (25).

There are two reports of correlation between ABHD2 and human cancer. In prostate cancer, ABHD2 was thought to promote cancer cell proliferation and migration (26); while suppression of ABHD2 led to chemoresistance and poor prognosis in ovarian cancer patients (27). Although there were no clues about how ABHD2 and GAS5 involved in their mutual regulation network of KIRC and LIHC, interestingly, our data implied that high GAS5 expression had lower DNA methylation status in tumor tissues compared to normal tissues in both KIRC and LIHC patients; while low ABHD2 expression had higher DNA methylation status compared to normal tissues in both KIRC and LIHC patients. Therefore, DNA methylation might regulate their transcriptions in both cancers.

To our knowledge, our research is the first to report that GAS5 might be involved with ABHD2 in KIRC and LIHC. Although the detailed molecular mechanisms remain unclear and need further verification, our findings demonstrated GAS5 as a prognostic marker for KIRC and LIHC, and could be useful for the development of biomarkers for those cancer treatments.

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Footnote

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